Introduction. The occurrence of peptic ulcer in patients with liver cirrhosis is intriguing due to its frequency and complexity. The aim of the present study was to investigate the incidence of peptic ulcer in patients with liver cirrhosis. Results. It was found that in these patients the usual aggressive factors of the gastric environment do not play a major role in ulcerogenesis; however, researches noticed the importance of reduced mucosal defense which, in portal hypertension, has the features of hypertensive portal gastropathy. The presence of Helicobacter pylori infection decreases with the severity of liver cirrhosis. Non-steroidal anti-inflammatory drugs play an important role in peptic ulcer bleeding in cirrhotic patients, but the data are limited and contradictory. Peptic ulcer bleeding is the most frequent etiology of nonvariceal bleeding and it is associated with a great number of complications. Conclusion. Helicobacter pylori infection cannot be considered the key risk factor for the development of peptic ulcer in patients with liver cirrhosis. The role of non-steroidal anti-inflammatory drugs is accepted, although the data are controversial. The treatment of peptic ulcer in cirrhotic patients is identical to the treatment of peptic ulcer in patients without liver cirrhosis, except in cases of bleeding ulcers. There are specific therapeutic protocols for peptic ulcer bleeding in patients with liver cirrhosis.

Global liver cirrhosis deaths increased from around 676,000 deaths in 1980 (1.54% of global deaths) to 1,029,042 deaths in 2010 (1.95% of the global total). In the Republic of Serbia, there were 822 deaths (537 – 1,212), 854 (607 – 1,185), 1,041 (833 – 1,378) and 951 (721 – 1,203) deaths (95% uncertainty intervals) in 1980, 1990, 2000, 2010, respectively [2].
Peptic ulcer (PU) is a continuous active disease with a significant social aspect. The cumulative prevalence of PU ranges from 8% to 14% [3].

Due to its incidence and complexity, the occurrence of PU in patients with LC has been intriguing clinicians and researchers for decades. The etiopathogenic mechanisms of PU in LC patients are not completely clear yet, as opposed to the incidence of PU in general population.

Earlier researches have established a connection between the severity of liver disease and PU incidence, and it was considered that the liver disease was the “primum movens” for PU, which was called “hepatogenic ulcer”. The clinical findings of increased incidence of PU in LC, despite reduction in gastric acid output, may be explained by relative disturbance of the balance between aggressive and protective mechanism, the latter being diminished [4].

The point prevalence of PU in patients with liver cirrhosis is 11.7%. The annual incidence of PU in these patients is 4.3%, with 2.8% accounting for duodenal ulcer (DU), and 1.4% for gastric ulcer (GU), which is 20 – 47 times higher incidence rate compared to the non-cirrhotic population [5, 6]. Other authors have found a similar point prevalence of PU in patients with liver cirrhosis, 10.5% [7], or even higher (24.3–38.5%) [8, 9].

A significantly higher prevalence of GU was found in patients with LC who have hepatic venous pressure gradient (HVPG) >12 mmHg, amounting to 20.8% compared to 4% in healthy controls [10].

The prevalence of GU in patients with LC is higher compared to the general population. Aggressive factors taking part in the pathogenesis of GU are lower, however, the defensive factors of gastric mucosa are also reduced due to portal hypertension (PH) [11].

In healthy (non-cirrhotic) population, the prevalence of GU accounts for 2% or less. Tomoda et al. found a prevalence of GU of 20% in patients with LC [12]. Other researches found the presence of GU in 15% of patients with decompensated LC and ascites, 3.3% in compensated patients, and 1.7% in healthy controls [13].

In patients with LC, the secretion of gastric acid (Hydrochloric acid - HCl) is reduced or possibly normal [14].

Tabaqchali and Dawson did not find a disorder of HCl secretion in patients with LC, except after portacaval anastomosis where it was found that basal secretion of HCl was increased, but without an accompanying increase to the maximum histamine stimulation [15].

Scobie and Summerskill found a significant decrease of basal and maximal (histamine stimulated) HCl secretion in patients with LC and concluded that this was not connected to the etiology or severity of the liver disease, nor with the presence or degree of the collateral portal circulation [16].

Lam examined the basal acid output (BAO) and the maximal acid output (MAO) after pentagastrin stimulation, and fasting and postprandial gastrin levels in patients with LC. The mean values of BAO and MAO were significantly lower compared to healthy controls. The fasting gastrin level was significantly higher, and the postprandial gastrin response was significantly increased and prolonged [17].

Gaur et al. examined the basal and pentagastrin-stimulated gastric secretion in patients with LC, in patients with non-cirrhotic portal fibrosis and in control groups. They found that the maximum volume and secretion of the gastric acid was significantly lower in the first two groups compared to the control groups. The authors did not establish a connection between the gastric hyposecretion and the degree of hepatocellular dysfunction, but they believed that the aforementioned could be secondary to portal hypertension and collateral circulation [18].

Savarino et al. examined 24-hour gastric pH-metry in patients with LC and found that these patients had significant hypoacidity during the entire circadian cycle compared to the control group of healthy subjects [19].

Patients with LC have normal basal pepsin levels, but a reduced response to stimulation. In patients with atrophic gastritis, pepsinogen levels are significantly lower in patients with LC compared to patients without liver diseases [20].

Classic aggressive factors of gastric environment, such as HCl and pepsin, do not have a significant impact on the pathogenesis of PU in LC.

Defensive Factors of Gastric Mucosa in PU Occurrence in Patients with LC

The increased susceptibility of gastric mucosal damage, associated with portal hypertensive gastropathy (PHG), usually caused by alcohol, aspirin and bile salts, was first described during the 1980s. Gastric mucosa in PH has PHG features with unique functional and morphological disruptions which make it susceptible to harmful agents. Such gastric mucosa has microvascular changes, even though the total gastric blood flow is unchanged. The essence lies in the redis-
ttribution of gastric blood flow with disrupted inflow of blood, and therefore oxygen in the gastric mucosa itself [21, 22].

Patients with LC and PH also have increased plasma endothelin-1 level, which is a powerful vasoconstrictor, as well as increased tumor necrosis factor-a, which has cytotoxic properties. The gastric mucus secretion, the content of gastric mucin and their precursor hexosamine, is reduced. Production of bicarbonates is also reduced. The mucosa of the stomach with PHG has a reduced proliferation of mucosal epithelial cells. The prostaglandin E2 content is significantly lower, especially in mucosal congestion. The increase in nitric oxide may contribute to the increased sensitivity to mucosal noxae in PHG [11].

**Ulcer Healing**

Proliferation of epithelial cells in the ulcer margin and angiogenesis at the bottom of the ulcer are essential for ulcer healing. The gastric ulcer healing in PHG is slow, primarily due to the inhibition of epithelial proliferation in the ulcer margin [23].

In the study of Siringo et al., after 8 weeks of therapy, GU healing occurred in 67% of patients with LC and 84% of patients without LC. Ulcer recurrence was higher in patients with LC (50%) than in patients without LC (30%) [5].

**Helicobacter Pylori Infection – the Role in Ulcerogenesis and PU Bleeding in Patients with LC**

*Helicobacter pylori* (H. pylori) is a human pathogen that is transferred from one human to another causing chronic active gastritis in all colonized subjects. This may lead to PU, atrophic gastritis, gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma. Eradication of H. pylori results in healing of gastritis and may prevent long-term complications of the infection [24].

In populations of Northern Europe and North America, about one-third of adults are still infected, whereas in south and east Europe, South America, and Asia, the prevalence of H. pylori is often higher than 50%. Low socioeconomic conditions in childhood are confirmed to be the most important risk factors for H. pylori infection [25].

In duodenal ulcer (DU), H. pylori infection is present in around 90 – 100% of cases, and in gastric ulcer (GU) in around 60 – 100% of cases. Eradication of H. pylori drastically reduces the annual recurrence of DU [26].

A lower incidence of H. pylori infection is recorded in PU bleeding (PUB). Authors from Novi Sad have found the presence of H. pylori in GU bleedings to be 58.33%, and 69.8% in DU bleedings [27]. They have also found that H. pylori per se is not a risk factor for PUB, but that it does have a synergistic effect with taking non-steroidal anti-inflammatory drugs (NSAIDs), OR = 3.63, p < 0.01. It was concluded that taking alcohol significantly increases the probability of PUB (OR = 3.25, p < 0.01) [28]. The use of alcohol in certain regions of Serbia is a significant problem [29].

H. pylori infection is significantly less present in patients with LC, even compared to the general population of medium-developed countries. Gastric mucosa in PHG is not a suitable element for H. pylori colonization. Colonization of gastric mucosa with H. pylori is 26% in patients with LC and PH, and 38% in patients without PH [30].

Alempijević et al. found that the infection with H. pylori is present in 36% of patients with LC, regardless of the presence of PU, and that in this case H. pylori infection does not impact the development of the ulcer disease [31].

Kim et al. found the presence of H. pylori infection in patients with LC and PU in 35.6% of cases, and in 34.9% of cases in patients with LC without PU. The presence of H. pylori infection decreases, and the frequency of PU increases proportionally to the severity of the LC [8].

Other authors have found PU incidence in a group of patients with LC, who were infected with H. pylori, to be eight times higher compared to the non-infected patients [32].

Certain researches show that H. pylori infection was present in 40 – 89% of patients with LC, which was probably conditioned by the methods used to establish the infection. Studies that used serological tests found greater incidence of H. pylori infection [13, 33, 34].

H. pylori infection rate in cirrhotic patients with PU is 35.5 – 51.92%. Although H. pylori is not the predominant etiologic factor of PU in LC, it should be treated. Early eradication of H. pylori infection is connected to the reduced risk of recurrent PU in patients with LC [35].

This is in contrast with the research done by Lo et al. who concluded that eradication of H. pylori infection in patients with LC and DU was not efficient in preventing ulcer recurrence [36]. In general population the approach to diagnostics and treatment of H. pylori infection significantly reduced the incidence of DU [37].

To sum up, the presence of H. pylori infection in patients with PU in LC is significantly lower compared to the presence of this infection in patients with PU without LC. The prevalence of H. pylori infection is not different in patients with LC with PU and those without PU. The prevalence of H. pylori infection decreases with the severity of liver disease, but there is no simultaneous change in the incidence of PU. Therefore, this infection cannot be considered one of the key factors of PU incidence in patients with LC.

**Non-steroidal Anti-Inflammatory Drugs: the Role in Ulcerogenesis and Peptic Ulcer Bleeding in Patients with Liver Cirrhosis**

Aspirin and other NSAIDs are a significant cause of PU in general population. Their use can be found in up to 60% of patients with PU [38].

In a study done by Bang et al., the prevalence of PU in LC was 18%. The prevalence of taking ulcer-
Peptic Ulcer Therapy in Patients with Liver Cirrhosis

Treatment of non-complicated PU in patients with LC is not different from treatment of PU in patients without LC. The therapy of PUB in patients with LC has its own specificities, regarding the basic liver disease.

It is necessary to point out the extensive application of PPI within chronic therapy of patients with LC without PU. These drugs are used by 25% to 40% of patients with cirrhosis without clearly documented indications. Without arguments for the application of these drugs, patients with LC are at risk for developing bacterial infections and sepsis with multiple organ dysfunction, deterioration of liver function and bad prognosis [48, 49].

Conclusion

In patients with liver cirrhosis there is a significant presence of peptic ulcer. Aggressive factors taking part in the pathogenesis of peptic ulcer are reduced, as well as defensive factors of gastric mucosa. *Helicobacter pylori* infection cannot be considered one of the key factors in the development of peptic ulcer in these patients. The importance of using non-steroidal anti-inflammatory drugs is undeniable, though controversial. Peptic ulcer appears more frequently in advanced liver cirrhosis. Peptic ulcer bleeding is the most frequent cause of non-variceal bleeding in these patients.

Treatment of non-complicated peptic ulcer in patients with liver cirrhosis does not differ from the treatment of peptic ulcer in patients without liver cirrhosis. The peptic ulcer bleeding in patients with liver cirrhosis has some specificities, regarding the basic liver disease.

It is necessary to point out the extensive application of PPI within chronic therapy of patients with LC without PU. These drugs are used by 25% to 40% of patients with cirrhosis without clearly documented indications. Without arguments for the application of these drugs, patients with LC are at risk for developing bacterial infections and sepsis with multiple organ dysfunction, deterioration of liver function and bad prognosis [48, 49].

Conclusion

In patients with liver cirrhosis there is a significant presence of peptic ulcer. Aggressive factors taking part in the pathogenesis of peptic ulcer are reduced, as well as defensive factors of gastric mucosa. *Helicobacter pylori* infection cannot be considered one of the key factors in the development of peptic ulcer in these patients. The importance of using non-steroidal anti-inflammatory drugs is undeniable, though controversial. Peptic ulcer appears more frequently in advanced liver cirrhosis. Peptic ulcer bleeding is the most frequent cause of non-variceal bleeding in these patients.

Treatment of non-complicated peptic ulcer in patients with liver cirrhosis does not differ from the treatment of peptic ulcer in patients without liver cirrhosis. The peptic ulcer bleeding in patients with liver cirrhosis has some specificities and therapeutic postulates. In the therapy of patients with liver cirrhosis without peptic ulcer, it is necessary to take a restrictive approach in applying proton pump inhibitors due to the risk for developing serious bacterial infections.
References


